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CIRCULATORY CHANGES IN THE 13-LINED GROUND SQUIRREL DURING THE HIBERNATING CYCLE

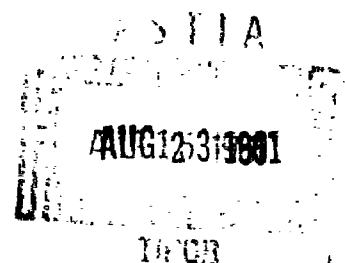
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ARCTIC AEROMEDICAL LABORATORY
FORT WAINWRIGHT
ALASKA



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ALASKAN AIR COMMAND
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ABSTRACT

This paper is a description of the changes which take place in the blood pressure, body temperature, and EKG during the hibernating cycle of the 13-lined ground squirrel (Citellus tridecemlineatus), and the effect of drugs during various parts of this cycle.

CIRCULATORY CHANGES IN THE 13-LINED GROUND SQUIRREL DURING THE HIBERNATING CYCLE¹

In the past few years the function of the heart in hibernation has received considerable attention. For example, it has been shown that there is a marked decline in heart rate before a decline in core temperature when the animal starts to enter the hibernating state (Lyman, 1958). In hibernation, the heart rate may vary greatly with no apparent changes in body temperature (Dawe and Morrison, 1955; Lyman, 1958). On arousal from the hibernating state, the heart rate increases prior to a change in body temperature (Lyman and Chatfield, 1950, and references above). These observations suggest that there must be important changes in the circulation during the hibernating cycle and that measurements of these changes might give further insight into the phenomenon.

Although some measurements have been made on the blood pressure of mammals waking from hibernation (Dubois, 1896; Chatfield and Lyman, 1950; Chao and Yeh, 1951), nothing has been reported on the blood pressure of mammals either entering the hibernating state or in natural, deep hibernation. The technique developed by Still and Whitcomb (1956) for chronically intubating the aorta of small mammals gave the opportunity of measuring the blood pressure of hibernators over long periods of time. Measurements could be made as the animal passed from the active condition into hibernation, as it remained in hibernation, and as it aroused from the hibernating state. The tube offered a means of introducing drugs of known pharmacological effect into the circulation at any point during the hibernating cycle without disturbing the animal. Using indwelling thermocouples and electrodes, the body temperature and the electrocardiogram (EKG) could be monitored concurrently with the blood pressure.

MATERIALS AND METHODS

A total of 47 ground squirrels were intubated for this study. Of these, five yielded satisfactory records of the various phases of the normal hibernating cycle, and seven others were used successfully in the study of the effect of drugs on the circulation during hibernation. Of the former,

¹Submitted for publication 25 April 1960.

continuous records of 2 to 8 days were obtained from single animals. The animals were kept in individual cages in a cold room which was maintained at $6^{\circ} \pm 4^{\circ}$ C. They were given shavings for bedding and Purina laboratory chow and water ad libitum. Animals which had hibernated over protracted periods of time were used preferentially.

Prior to intubation, the animals were aroused in a warm room, and then anesthetized with an intraperitoneal injection of pentobarbital sodium (80 mg/kg). The aorta was exposed by an abdominal incision. A small slit was made in the vessel about 1 cm posterior to the renal arteries, and a thin polyethylene tube (PE 10, ID .28 mm, OD 0.6 mm), bevelled at the end, was inserted into the slit and pushed rostrally 1.5 cm. No modifications were made in the technique described by Still and Whitcomb (1956) except that the instrument used to make the slit in the aorta was a curved Bard Parker blade (size 12) ground to 0.5 mm width and sharpened to a needle-like point. Once the tube was fastened in place with a tie to the muscles of the back, it was filled with heparin-saline (25 mg heparin/10 ml physiological saline) and closed at the distal end with a knot. The abdominal incision was closed and the tube anchored again with a tie at the caudal edge of the incision. The tube was then led subcutaneously to an exit between the scapulae, and fastened to the skin of the back. The animal was given 40,000 units of procaine penicillin and returned to its cage in the cold room.

If intubated animals were observed to re-enter hibernation, they were removed in the hibernating state and fitted with one or two thermocouples made of 34-gauge iron and constantan wire individually protected with PE 10 polyethylene tubing. Usually one thermocouple was fastened subcutaneously in the region near the heart and the other fastened intraperitoneally at the mid-abdomen. The thermocouple wires were led subcutaneously to the exit between the scapulae. Three silver wire electrodes were sewed into the skin of the back. The tube in the aorta was spliced using a section of No. 27 hypodermic needle and a long piece of PE 10 tubing. All wires and the tube were passed through a helical spring for protection, and the spring was sewed to the back where the tube and thermocouple wires made their exit from the animal.

The ground squirrel was placed in a round battery jar measuring 23 cm in diameter, with food and water and the bedding from its cage. The helical spring was led through a wire screen which closed the top of the jar and was suspended with an elastic band so that the animal could move freely in the cage without being bothered by the cable.

Throughout the chronic experiments, temperatures from the heart and the abdomen were each recorded every 32 seconds on a Leeds and Northrup

Speedomax thermoelectric recorder with an accuracy of $\pm 0.25^{\circ}$ C. The EKG and blood pressure were obtained every 4 minutes for a period of 1 minute.

Blood pressure was measured directly from the polyethylene tube using a Statham P23D pressure transducer². This was amplified with a Grass low-level DC preamplifier, model 5P1A, and Polygraph DC driver amplifier, model 5³. Various sensitivity settings were used during the experiments, and a drift of as much as 25 mm Hg could take place in a 24-hour period. However, the machine was calibrated at least twice a day, and more often when exact measurements were required. Thus, the accuracy did not vary more than ± 5 mm Hg which is a slight change compared to those which actually took place in the blood pressure. In order to prevent clotting in the tube, a flow of heparin-saline (0.6 mg/ml) of approximately 0.5 ml per day was perfused through the tube by means of a slowly driven screw-drive syringe. Because it was possible that the length of the polyethylene tube might seriously affect the recorded pulse pressure, various lengths of tubing were tried under known conditions of blood pressure. It was found that, within the conditions of the experiment, neither the varying lengths nor the temperatures of the tubes made any appreciable differences in the blood pressure measurements.

The apparatus was kept running day and night during the measurements. At various times, records were obtained of animals in the active condition in the cold, during the process of entering hibernation, in the hibernating state, and arousing from hibernation.

In the experiments using drugs, the agent was introduced into the animal via the polyethylene tube. In all cases, the approximate dosage was determined by giving graded doses of the drug in question to intubated, nembutalized rats. Awake, intubated ground squirrels were given doses below those which affected the rats, and the dosage was increased until some effect was noted. Subsequently, a comparable dose was used initially in each experiment and increased gradually if no effect was noted. Periodically, tests were made to be sure that the same amount of heparin-saline solution did not produce a similar result. In order to produce vasodilation, individual doses of acetylcholine chloride (Merck⁴) varying from 0.15 to 1.2 mg/kg were given while benodaine hydrochloride (Merck⁵) was given at 8 to 41 mg/kg.

²Statham Instruments Inc., Los Angeles, California.

³Grass Instrument Co., Quincy, Mass.

⁴We are extremely obliged to Merck and Co. of Rahway, New Jersey, for giving us the acetylcholine.

⁵2-(1-Piperidylmethyl)-1,4-benzodioxan hydrochloride.

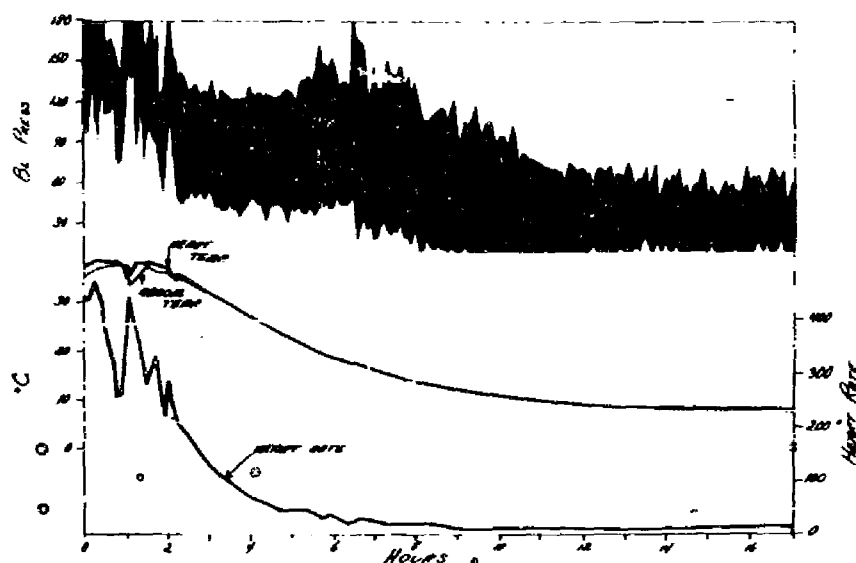


Figure 1. Blood pressure, heart and abdominal temperature, and heart rate of ground squirrel entering hibernation. Blood pressure in dark area is highest systole and lowest diastole recorded every 4 minutes for a 1-minute period. Note declines in heart rate and blood pressure, followed by body temperature.

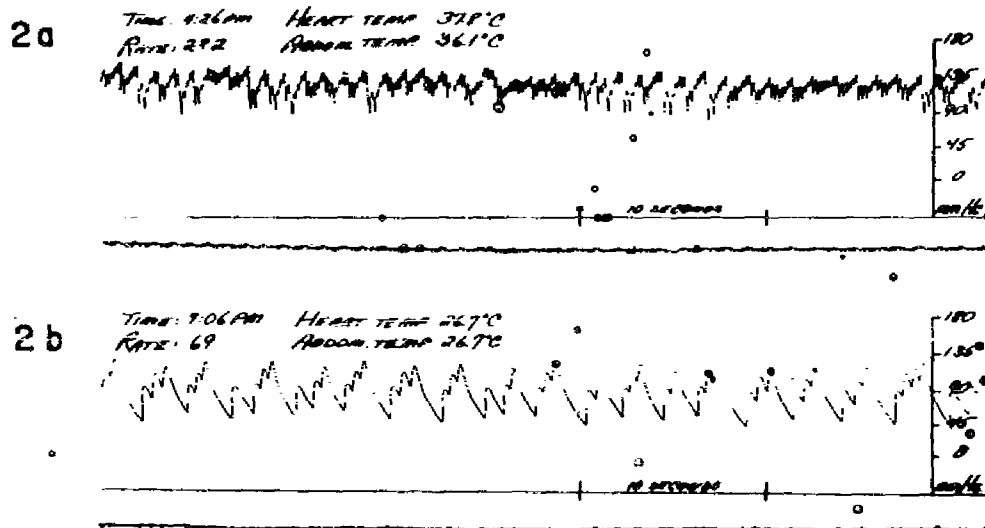


Figure 2a. Blood pressure and EKG of same animal starting to enter hibernation. Note uneven pattern of beats, 4:26 p.m. - 1 1/2 hours on Figure 1.

Figure 2b. Same animal later. Note even pattern of beats and skipped beats.

To produce vasoconstriction, l-norepinephrine (Levophed bitartrate, 0.2%, Winthrop) was used in concentrations of 6 to 44 $\mu\text{g/kg}$.

RESULTS

The normal nonhibernating ground squirrel in the cold maintained a fairly steady heart temperature of $37^{\circ} \pm 1^{\circ} \text{C}$. The abdominal temperature averaged from 0.5° to 1°C below the heart temperature. Blood pressure and heart rate varied considerably, depending chiefly on the activity of the animal. Often the heart rate was reduced as much as one-half in a few seconds, accompanied by a reduced blood pressure and an increase in pulse pressure. Though this occurred invariably if the animal were alarmed, it also took place for no apparent reason. Over periods when two animals failed to hibernate for several days, the mean blood pressures averaged 119 mm Hg, but the highest mean pressure was 158 and the lowest was 76. Highest systolic and lowest diastolic pressures were about 20 mm Hg above and below these figures. Heart rates from the same observations averaged 299 beats per minute, with a high of 468 and a low of 184.

Entrance into hibernation was usually preceded by some sort of activity, for the blood pressure and heart rate rose transiently. After this period of activity, there was a sudden drop in heart rate, accompanied by a decrease in systolic and diastolic pressure (Fig. 1). Although the heart rate might decrease to one-third of its original value in 15 minutes and the blood pressure drop precipitously, still the latter remained in the lower part of the range found in the resting, awake animal.

After heart rate and blood pressure declined, the body temperature started to decrease. Often after a few minutes the heart rate again speeded, and the blood pressure rose. This was followed by a rise in body temperature. A second decline in heart rate and blood pressure was again followed by a drop in body temperature. Although the heart and abdominal temperatures were not the same at the beginning of the hibernating state, they soon became identical and remained the same until the animal was near the temperature of the environment. At this time, the heart temperature was about 0.5°C above the abdominal temperature and remained so while the animal stayed in hibernation.

During the first part of entrance into hibernation, the heart rate and blood pressure were irregular. Bradycardia often occurred for a few

seconds followed by tachycardia, with a concurrent decline and rise in blood pressure (Figs. 1 and 2a). As the entrance into hibernation proceeded, the pattern of the heart rate became more regular, and the fluctuations in blood pressure became less pronounced. Thus, when the heart temperature reached the range from 32° to 21° C, the graph of highest systole and lowest diastole became much more even (Fig. 1). Slowing of the heart was accomplished both by quite evenly occurring skipped beats and by reduction of the even rate of the heart (Fig. 2b). Occasionally, while the body temperature was still dropping, the heart rate increased transiently and muscle action potentials appeared on the EKG. An increase in heart rate and a rise in blood pressure occurred at the same time (Fig. 3a). Such transient bursts of activity occurred at unpredictable intervals and usually lasted too short a time to cause any difference in the decline in the body temperature, but occasionally, they were of longer duration and actually resulted in a brief rise in body temperature. Also as hibernation deepened, the heart rate became slower and the pulse pressure increased (compare Figs. 2a, 2b, and 3a). These changes were accompanied by a slight lengthening of systole and an increasingly long diastole (compare Figs. 2 and 3, a and b).

The marked increase in the length of diastole indicated an increase in peripheral resistance as hibernation deepened. Because the systolic pressure varied greatly, it was possible to compare the rate of diastolic runoff from the same systolic pressure at all stages of the entrance into hibernation. If the increase of the angle which the diastolic pressure made with the perpendicular was plotted against temperature, the result was almost a straight line.

In deep hibernation two or more heart beats sometimes occurred quite close together, followed by a long diastole. In such cases, the second beat occurred before diastolic pressure had sufficient time to drop markedly, and the next systolic pressure was higher than the first (Fig. 9c). This implies that there was considerable blood in the heart after the first beat. At other times, the heart rate was fairly regular, though it was never absolutely even. In this case, systolic pressure rose to about the same height with each beat, and the drop in pressure during the latter part of diastole was so slow, as the blood pressure approached zero, that diastolic pressure remained extremely even. In the whole series of records, the systolic pressure varied between 90 and 40 mm Hg and the diastolic between 40 and below 10 mm Hg, with heart temperatures between 5° and 8.3° C. The lowest precise record of diastolic pressure was 7 mm Hg. Very long-term records of animals in hibernation were not made, but heart rates as low as three beats per minute were recorded.

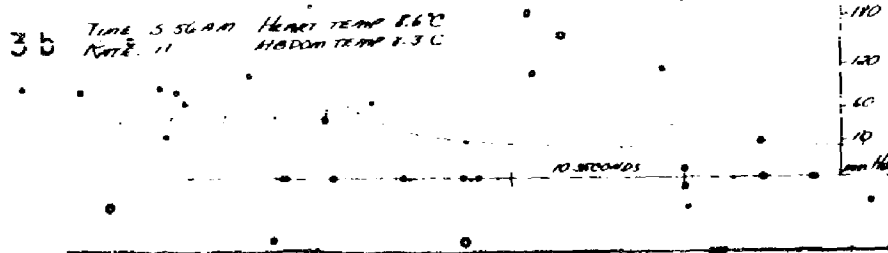
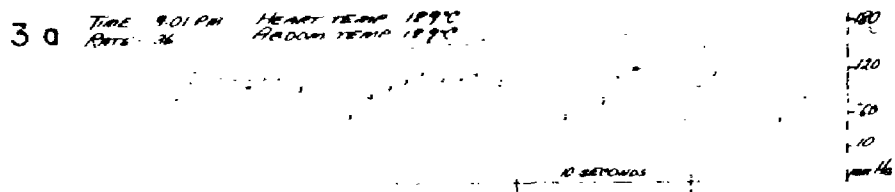


Figure 3a. Same animal as in Figure 2, showing transient increase of heart rate at low body temperature. Note muscle action potentials on EKG.

Figure 3b. Same animal, now in deep hibernation. Blood pressure tube slightly plugged. Blurring of EKG is electrical artifact.

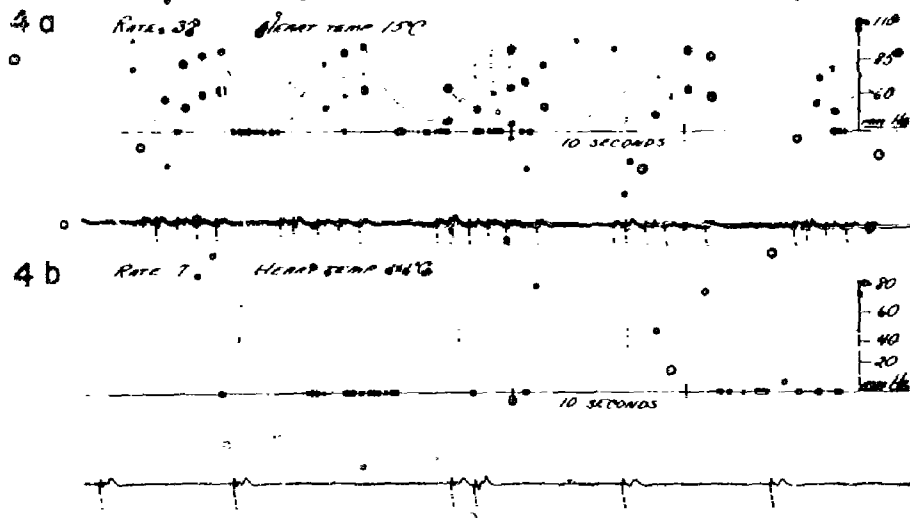


Figure 4a. Another animal entering hibernation. Evenly occurring electrical depolarizations with little or no change in pulse pressure.

Figure 4b. Extra systole with no change in pulse pressure. Rates measured by EKG.

Occasionally, as the animal entered hibernation, or when in deep hibernation, complete sequences of myocardial depolarizations were recorded with little or no change in pulse pressure. These sometimes occurred at fairly evenly spaced intervals (Fig. 4a) with slight changes in the configuration of the EKG, and at other times took the form of extra systoles (Fig. 4b) with no change in pulse pressure.

Complete records were obtained of animals which were stimulated to arouse them from the hibernating state (Fig. 5). In some cases the animals were stimulated by poking, but in those animals which were fitted only with a heart thermocouple, arousal was initiated by the insertion of a rectal thermocouple to a depth of 2.5 cm.

As soon as the animal was disturbed, the heart rate increased and diastole was markedly shortened. The increase of heart rate was accompanied by the appearance of muscle action potentials (Fig. 6a). These changes were often observed within 2 or 3 minutes after application of the stimulus. Later, systolic and diastolic pressures rose and the heart began to warm (Fig. 6b).

As arousal continued the heart rate became more rapid, the blood pressure rose, and violent shivering could be seen in the anterior part of the animal. Although the plot of the highest systole and the lowest diastole does not show it clearly (Fig. 5), the pulse pressure was considerably reduced (Fig. 7a). During this time, the temperature of the heart and the anterior part of the body increased rapidly, while the abdominal temperature remained nearly static (Fig. 5).

As the heart temperature approached 37° C, the abdominal temperature started to rise and the blood pressure and heart rate usually, but not invariably, dropped from the extreme heights to which they had climbed (Figs. 5, 7a, and 7b). During this time diastolic runoff was more rapid, indicating a decrease in peripheral resistance. The abdominal temperature rose rapidly, and within 2 1/2 to 3 1/2 hours after the initial stimulus, the animal was completely aroused. For an hour or more after this, the heart and rectal temperatures averaged at least a degree above that found in the normal, awake animal.

A single record of an animal which started to arouse spontaneously at 2:30 a. m. showed the same sequence of events, with heart rate and blood pressure rising before heart temperature.

Occasionally during the winter months an animal, when stimulated during hibernation, started the arousal process, but did not complete it and

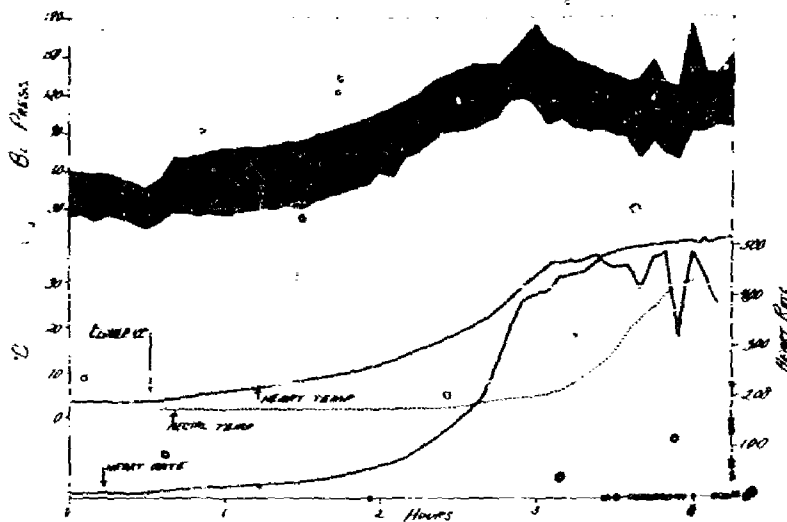


Figure 5. Animal waking from hibernation, graphed as in Figure 1.

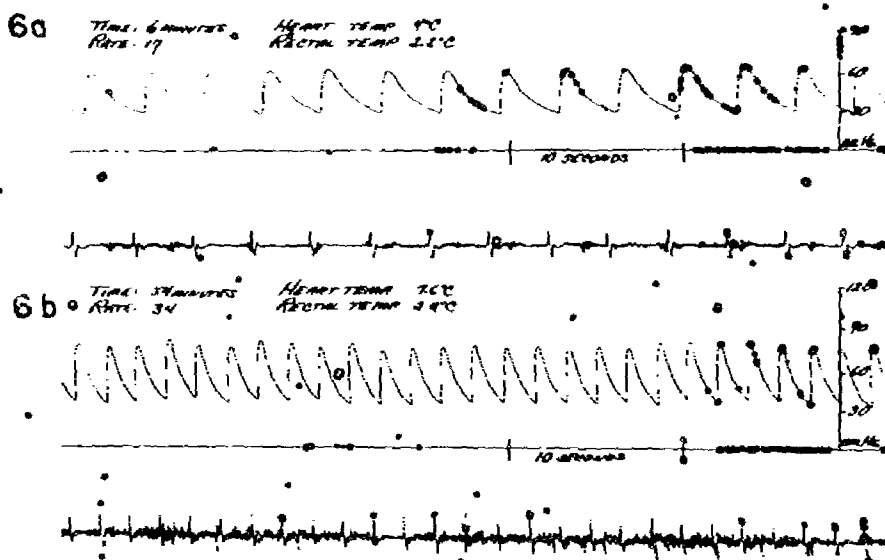


Figure 6a. Same animal as in Figure 5. Note bursts of muscle action potentials in EKG. Time = minutes after animal was picked up.

Figure 6b. Same animal. Note increase in systolic pressure, heart rate, and muscle action potentials.

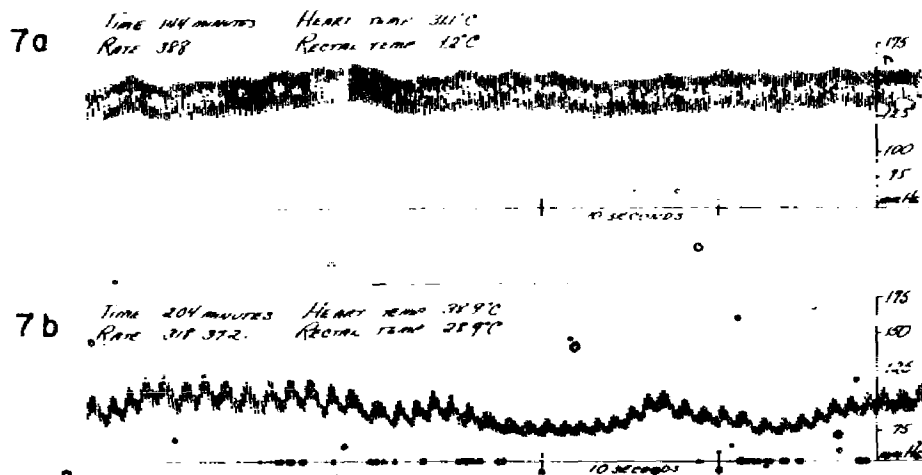


Figure 7a. Same animal, before posterior has warmed. EKG discontinued because of fast rate and blurring by muscle action potentials.

Figure 7b. Same animal. Posterior now warming. The even variation in blood pressure is caused by respiration.

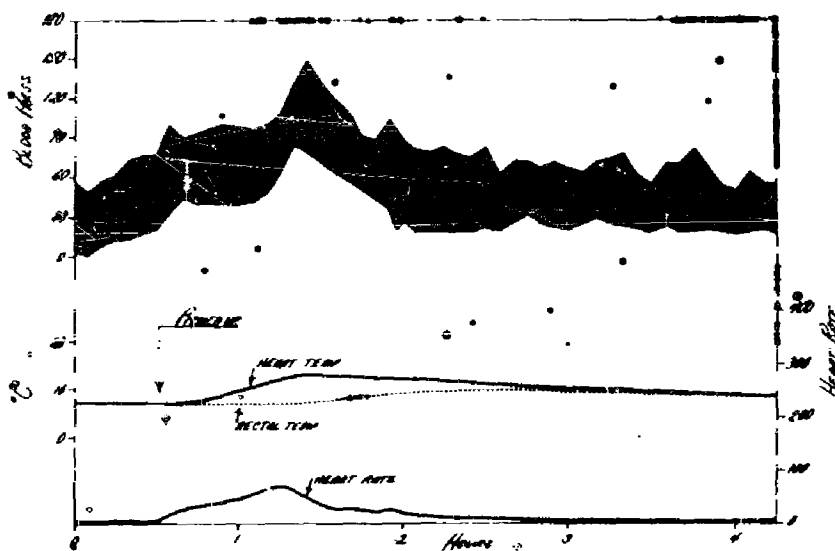


Figure 8. Graph of partial waking and re-entrance into hibernation, as in Figure 1.

returned to the hibernating state (Fig. 8). In these cases the arousal was precisely as described above, with a rapid rise in heart rate, blood pressure, temperature, and frequency of muscle action potentials. Quite suddenly, however, the heart slowed and the muscle action potentials were reduced. Peripheral resistance, as measured by the slope of the diastolic runoff time as described above, increased. The blood pressure dropped, but not as rapidly as the decrease in heart rate. As the animal re-entered the hibernating state, the heart temperature declined slowly and the abdominal region, which had remained cold during the transient period of arousal, rose slowly to nearly the temperature of the heart and then declined with the heart temperature.

REACTION TO DRUGS

When the experiments with drugs were begun, it was apparent that the heart of the hibernating animal was extremely sensitive to liquids introduced via the intubated aorta. As little as 0.07 ml of physiological saline introduced quickly occasionally caused a slight transient increase in heart rate. For this reason, the effect of the drugs was repeatedly checked against control injections of saline solution. Although the same drug was often used several times on a single animal, every experiment was repeated on at least two animals.

Acetylcholine

As might be expected, fairly large doses (0.15 to 0.9 mg/kg) of acetylcholine were necessary to override the presence of cholinesterase in the awake ground squirrel and cause a clear-cut effect. Once the effective dose was reached, there was a drop in blood pressure and a compensatory increase in heart rate of 55% to 70%. There was not observed bradycardia caused by this drug.

Similar dosage produced a marked effect on the hibernating animals. This effect consisted of a rapid decrease in peripheral resistance coupled with a rise in heart rate. Unlike the situation in the awake animal, the systolic and diastolic blood pressure showed little or no change during this time (Figs. 9a and 9b). If the infusion of acetylcholine was continued, the heart rate increased further and the animal started the process of arousal. Although the long-term effect of acetylcholine is typical of a normal arousal,

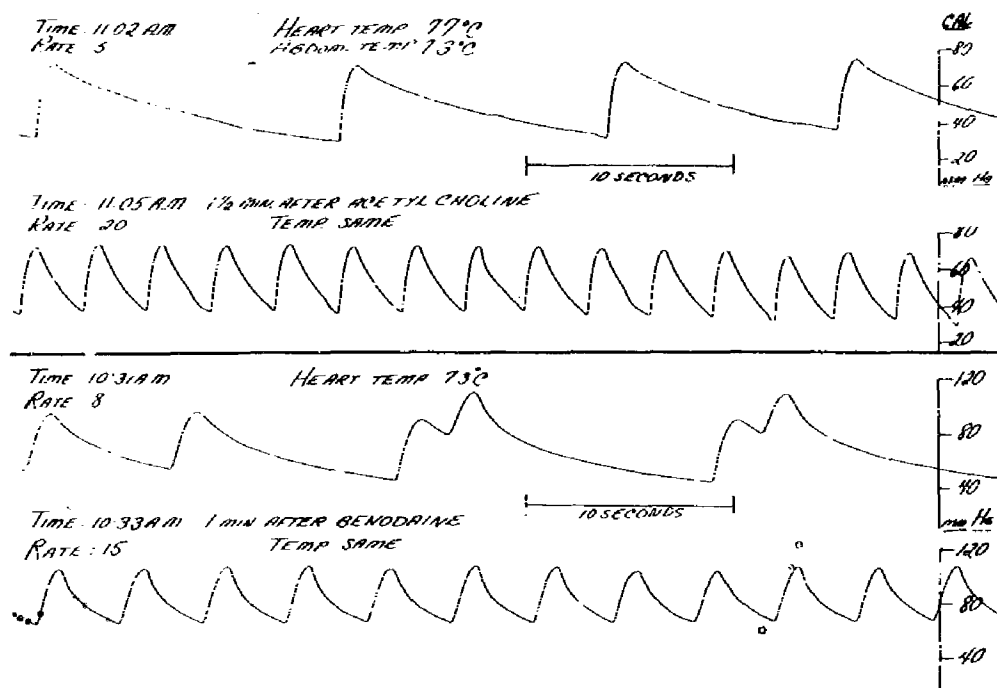


Figure 9a. Pulse pressure in deep hibernation.

- Figure 9b. Pulse pressure after acetylcholine. Note faster diastolic runoff from slightly lower systolic pressure than in Figure 9a.

Figure 9c. Pulse pressure in deep hibernation.

- Figure 9d. Pulse pressure after Benodaine hydrochloride. Note faster diastolic runoff after same systolic pressure.

we were not able to determine whether this drug is actually the neurohumoral agent which mediates the waking process. It is possible that vasodilation and speeding of the heart, were in themselves as much of a stimulus to waking as would be an externally applied physical stimulus. However, within the range of the dosage used, short-term, rapid injections of acetylcholine did not cause arousal, while one sharp mechanical stimulus almost invariably produced this result.

Acetylcholine had apparently no effect on the distribution of blood once arousal was fully underway, for doses as large as 2.32 mg/kg failed to cause a change in the blood pressure or a rise in the abdominal temperature.

Benodaine hydrochloride was chosen as an adrenergic blocking agent rather than dibenamine hydrochloride (Merck), or other of the better-known drugs, because its effect is of short duration (Goodman and Gilman, 1958). In low dosage, the primary effect of this drug was a speeding of the heart and a resulting rise in blood pressure in both the awake and hibernating animals. Larger dosage caused a drop in blood pressure in the awake animal, although the heart rate was increased. In the hibernating animal doses of 8.5 to 25 mg/kg caused a marked decrease in diastolic runoff time along with an increase in heart rate (Figs. 9c and 9d).

Norepinephrine infused rapidly into the active ground squirrel caused a rise in blood pressure, an increase in pulse pressure, and a slowing of the heart which was probably compensatory. In contrast, the effect of this drug on the hibernating animal in doses of 6 to 20 μ g/kg was an increase in heart rate and pulse pressure and a rapid rise in blood pressure. Because of this rapid rise, sufficient comparative measurements of diastolic runoff time could not be made, but there was no evidence that peripheral resistance was increased by norepinephrine during hibernation. The rise in heart rate and pulse pressure alone were enough to account for the initial rise in blood pressure.

Norepinephrine at doses of 17 to 44 μ g/kg was also introduced into animals during arousal, when the heart temperature had reached 37° C and the temperature of the posterior part of the body had started to rise. At this time, the drug caused an immediate rise in blood pressure, and the abdominal temperature ceased rising and remained level for 1 minute or more. After this time, the blood pressure resumed its original level and the abdominal area again started to warm. It was not possible to hold the blood pressure at the high level or to stop the abdominal region from warming over long periods of time in spite of the infusion of large amounts of norepinephrine. However, the abdominal temperature could be made to rise in a stepwise fashion by periodic introductions of norepinephrine into the bloodstream.

DISCUSSION

Records of blood pressure in any stage of hibernation are scanty, and none have been reported on mammals entering hibernation or in the undisturbed hibernating state. Dubois (1896) reported very low blood pressures after the cannulation of the carotid artery in the hibernating marmot. Blood pressure became higher as the animal aroused from the hibernating state, but Dubois did not trace the changes during the arousal process. Chao and Yeh (1951) measured the blood pressure of hibernating hedgehogs by acute cannulation of one carotid artery. The conditions of the experiment were very different from those described here, as the animals were strapped to a board throughout the experiment. These authors report that the carotid arteries were completely bloodless during hibernation, which is certainly not the case in hibernating rodents.

Chatfield and Lyman (1950) measured the blood pressure of hamsters arousing from hibernation by acutely cannulating a carotid artery. The conditions of the experiments were comparable to those reported here for the process of arousal, except that there was a time lag of 25 to 35 minutes to perform the cannulation. The results differ in that the rise in blood pressure was much more rapid in the hamster, but did not reach the high pressures observed in the waking ground squirrels. The observations on hamsters should be repeated using chronic intubation, not only to clarify this discrepancy, but also because the variations in the physiology of hibernation in these two species should supply interesting comparisons on the condition of the circulation.

As far as the present results are concerned, it is apparent that there is a decrease of heart rate and blood pressure as the ground squirrel enters hibernation, and that this decrease occurs before a detectable decrease in body temperature. The equal temperatures of heart and abdomen as the animal enters the hibernating state indicate that blood flow to the anterior and posterior parts of the body is evenly distributed. As body temperature drops, peripheral resistance increases. A part of this increase in peripheral resistance is probably caused by the increased viscosity of the chilling blood. However, part of the resistance must be caused by changes in the vascular bed for the stimulus of waking, as a vasodilatory or an adrenergic blocking drug, can quickly reduce the peripheral resistance before there is any measurable change in temperature.

The result of the increased peripheral resistance and concurrent rise in pulse pressure is that the mean blood pressure remains at remarkably high

levels, even with a heart rate of only three or four beats per minute in the deeply hibernating animal. We have observed in chilled, nembutalized ground squirrels that the peripheral resistance does not rise appreciably as the animal cools, nor does the pulse pressure increase. The net result of a low systolic pressure and a rapid diastolic runoff time is a very low mean blood pressure. This may contribute to the early death of the hypothermed potential hibernator, while the animal in natural hibernation may live for many days.

The great increase in peripheral resistance with hibernation was unexpected. From our observations on the equal rate of decline of temperature in various parts of the woodchuck (Lyman, 1958), we had postulated that the animal was vasodilated as it entered hibernation. It appeared reasonable that any vasoconstriction would cause marked differences in temperature in various parts of the body as observed in the waking hibernator. The possibility of a gradual, evenly distributed, vasoconstriction over the whole body had not even been considered. It now appears likely, however, that the hemodynamics of the ground squirrel and the closely related woodchuck during the hibernating cycle are identical, for in both animals the temperature distribution is the same on entering and waking from hibernation and in both, the heart rate anticipates any change in temperature.

The hibernating 13-lined ground squirrel is therefore probably evenly vasoconstricted over its whole body. Prior to any measurements of blood pressure in hibernation, we had suggested that the pink feet of the hibernating hamster might indicate a condition of vasodilation (Lyman and Chatfield, 1955). Although hibernation of hamsters and ground squirrels differs in many ways, an alternative explanation for the pink feet of the hamster could be the cherry-red condition of the blood during hibernation.

In the case of extra systoles (Fig. 4b), the presence of electrical depolarization of the heart during hibernation, with little or no change in pulse pressure may be explained by a lack of filling time before the next beat. When depolarizations occurred at more even intervals (Fig. 4a), some effect of the deep respirations of hibernation might have reduced or obliterated the arterial pulse. On the other hand, depolarization without visible beats in isolated hearts of the ground squirrel (Landau, 1956) and hamster (Lyman and Blinks, 1959) have been reported, and complete uncoupling of the membrane phenomena and the contractile process are at least theoretically possible (Brooks, *et al.*, 1955, p. 317). Whatever the explanation, it is interesting that the effective arterial pulse in hibernation can be even less than the very slow electrically measured heart rate.

When the hibernating ground squirrel starts to arouse, there is a rapid rise in heart rate and decrease in peripheral resistance. Similar results may be produced by vasodilatory drugs. In neither case is it possible to tell whether the decreased peripheral resistance causes a compensatory speeding of the heart, or whether the decrease in peripheral resistance and increase in heart rate occur at the same time. Shortly thereafter, the heart starts to warm though the posterior remains cold.

One is forced to conclude that there is a differential vasodilation in the anterior part of the body which is a vital part of the waking process. That vasodilatory drugs do not cause a warming of the posterior part of the body suggests that vascular beds of the anterior and posterior parts have different thresholds at this stage in the hibernating cycle.

Although peripheral resistance is reduced as arousal starts, the heart is able to maintain the blood pressure by increasing its rate. Indeed, as arousal progresses, the blood pressure rises and the heart rate increases, in spite of an ever decreasing peripheral resistance. The confinement of the active circulation to the anterior part of the body results in high blood pressure and efficient and rapid warming of this area. In contrast, if an active ground squirrel is given acetylcholine, the result is a drop in blood pressure, even though the heart may almost double its rate. Evidently the heart cannot maintain a high blood pressure when the whole capillary bed is vasodilated at the same time.

A similar condition is found in animals during the later stages of arousal from hibernation. During this time, the posterior portion of the animal is warming rapidly, indicating an unrestricted blood flow. The blood pressure, which reached its height when the anterior part of the body was still warming, now decreases because of the increase in the amount of open vascular bed. If norepinephrine is injected at this time, the blood pressure increases temporarily and the abdominal temperature remains static for a short time. One can thus produce with a vasoconstrictor the condition which obtained early in the waking process, but this condition cannot be maintained for long.

The fortuitous observations of partial arousals from hibernation fill out the general picture developed here. The arousal is normal until the heart begins to slow and the blood pressure drops. The fact that the blood pressure does not drop as fast as the heart rate indicates that peripheral resistance must now be increasing in the anterior part of the body. Since the posterior part of the body warms very slowly, circulation of blood between anterior and posterior must be sluggish, which emphasizes that the peripheral resistance in the latter must be high.

The picture during the hibernating cycle is of a circulation under remarkably precise control at all times. With our present knowledge, we can only speculate about mechanisms which cause the observed changes. However, it seems clear that shifts in temperature alone do not mediate the complex interrelationships. Furthermore, whatever is controlling the heart, this organ is remarkably sensitive to stimuli at all stages of the hibernating cycle. Further study is in progress with other pharmacological agents in an attempt to clarify these problems.

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